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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,668	03/19/2004	William A. Zoghbi	HO-P02680US1	8004

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EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/804,668	ZOGHBI ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *1-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

The text of those sections of 35 U.S.C. not included in this action can be found in a prior office action mailed 18 April 2006.

Objections Withdrawn

Specification

The objection to the specification because the abstract contained the phrase "said cardiac stress" is withdrawn in response to Applicants' amendment of the abstract filed 18 August 2006.

Information Disclosure Statement

The objection to the IDS filed 18 May 2005 because citations BA, CC, CD, CE, CF, CG, CH, CK, CL, CM, CO, CQ, CR, CS, CT, CU, CV, CX, CZ, CA1 and CB1 did not have full copies of the references has been withdrawn in response to Applicants' submission of copies of those references. Note that only those references that were objected are hereby considered.

Rejections withdrawn

Claim Rejections - 35 USC § 102

The rejection(s) of claim(s) 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 36, 40, 41, 42, 43, 44 under 35 U.S.C. 102(b) is

withdrawn in response to Applicants' argument that "immediately post cardiac stress" is not encompassed by 30 minutes post-cardiac stress (as taught in Marumoto).

Response to Arguments/New Rejections

Claim Rejections - 35 USC § 103

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 36, 40, 41, 42, 43, 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marumoto et al. (cited in previous Office action mailed 18 April 2006).

The claims recite a method of detecting coronary artery disease (CAD) in a human with no known history of a previous myocardial infarction, but with at least one cardiac risk factor as recited in claim 8, comprising measuring BNP in the human by immunoassay at baseline, inducing cardiac stress via exercise testing (treadmill or bicycle test), wherein a single photon emission computed tomography test is co-administered during induction of cardiac stress, measuring BNP about 10-15 minutes post-cardiac stress, calculating a relative change in the marker related to BNP wherein CAD is detected if the relative change after cardiac stress is greater than predetermined clinically effective values.

As stated above, Applicants' argument that Marumoto et al. do not teach the measurement of BNP ***immediately*** post cardiac stress, see p. 4, 3rd paragraph, filed 18 August 2006, with respect to the rejection(s) of claim(s) 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 36, 40, 41, 42, 43, 44

under 35 U.S.C. 102(b) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the fact that Figure 2 of Marumoto clearly suggests that taking BNP levels any time from peak exercise to 30 minutes post-exercise would show a difference in BNP levels between healthy and heart diseased patients.

Marumoto et al. teach a method of measuring BNP by radioimmunoassay at baseline (*i.e.*, a predetermined clinically effective threshold value—no other predetermined clinically effective threshold value is defined in the specification) in humans suspected of having CAD with at least one of the risk factors of CAD as recited claim 8 (*e.g.* age greater than 35 years), but with no history of myocardial infarction, inducing cardiac stress via exercise testing and co-administering a single photon emission computed tomography test, measuring BNP 30 minutes post cardiac stress, and correlating BNP measurements with severity score in patients with chest pain, wherein BNP levels reflected acute myocardial ischemia in patients with chest pain (see p. 551-553, entire section under Materials and Methods; p. 554, Figure 2 and left column, 4th paragraph). Myocardial ischemia represents a pathological development in the course of coronary artery disease, thus inherently represents a stage in CAD. Applicants do not define the "predetermined clinically effective threshold value" in the specification as a number, but rather, in broad terms to indicate that the value may be adjusted depending upon whether one is seeking greater sensitivity or specificity of the clinical test (see [0058]). No number value is given, thus the resting BNP levels recorded in Marumoto et al. could serve as a threshold value. Marumoto et al. do not

teach measuring BNP immediately post cardiac stress (defined in the specification as 1-3 minutes post-cardiac stress and in claim 5 as "about 10-15 minutes post cardiac stress".

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Marumoto et al. by measuring BNP immediately post cardiac stress (or any time-point between peak exercise and 30 minutes post-cardiac stress) because Figure 2 of Marumoto et al. strongly suggest that the BNP levels could be measured any time from peak exercise to 30 minutes post cardiac stress, because the difference in BNP levels would be much greater between heart diseased and normal subjects immediately post cardiac stress than 30 minutes post stress. Although Marumoto et al. show a statistically significant difference between healthy and diseased individuals at 30 minutes post-cardiac stress, Figure 2 suggests that this difference would be greater if the measurements were taken immediately post-cardiac stress. For this reason as well, the person of ordinary skill in the art would have been strongly motivated to change the measurements from 30 minutes post-cardiac stress to immediately post cardiac stress, namely the differences measured at the earlier time-point would be so much greater, that fewer false negatives would occur in a diagnostic test where the measurements of BNP were made immediately post cardiac stress. Furthermore, the person of ordinary skill in the art could have reasonably expected success because Figure 2 strongly suggests that measuring BNP levels immediately post-cardiac stress would show that there are differences between diseased and healthy subjects immediately post-cardiac stress.

Claims 18-22 recite the method of claim 1, wherein: the relative change in the marker related to BNP is from about 10% (claim 18) 10% to about 400% (claim 19), at least about 1% per minute of exercise (claim 20), at least about 5% per minute of exercise (claim 21) and about 5% to about 27% per minute of exercise (claim 22). Marumoto et al. teach the same method steps as recited in the instant claim 1 with the exception that the measurement of BNP levels was taken 30 minutes post-cardiac stress rather than immediately post cardiac stress. Nevertheless, Marumoto et al. strongly suggest that BNP levels would be significantly different between diseased and normal patients immediately post-cardiac stress, thus this suggests the limitations recited in claims 18-22 would by necessity inherently be met by Marumoto et al., although they are silent with respect to the specific values taught in the claims. Marumoto et al. teach all the same method steps with the exception that measurement of BNP levels immediately post-cardiac stress is strongly suggested rather than actually done, in the same population of patients, and the results of Marumoto et al. predicted severity of CAD. Similar reasoning is applied to claims 23 and its dependent claims, which further recite that the relative change in the maker related to BNP level correlates with severity of CAD. Marumoto et al. state on p. 555, middle of the 1st paragraph, that plasma BNP levels at peak exercise may reflect the severity of myocardial ischemia, thus the method as taught could be used to diagnose CAD and the conclusions drawn by Marumoto et al. (exercising BNP levels are higher in those individuals with chest pain) could be used in risk stratification.

Thus the claims are obviated by the prior art teaching of Marumoto et al.

The arguments presented by Applicants are mostly directed toward the rejection under 35 U.S.C. 102(b), and since that rejection has been dropped are not relevant to the new rejection under 35 U.S.C. 103(a), however, at pps. 4, last paragraph, p. 5, 4th - 5th paragraphs, Applicants assert that Marumoto et al. do not teach measuring a relative change in BNP level, defined as the change in the BNP level immediately after exercise as compared to the baseline level, which is defined as the BNP level before a specific event, for example, the BNP level after exercise is compared to a baseline BNP level before exercise. This argument has been fully considered but is not found persuasive because Figure 2 of Marumoto et al. clearly suggest that there is a relative change in BNP levels between diseased and normal subjects, defined as the change in the BNP level immediately after exercise as compared to the baseline level, which is defined as the BNP level before a specific event, for example, the BNP level after exercise is compared to a baseline BNP level before exercise.

In addition, Applicants are reminded that the rejections under 35 103(a) below were built upon the rejection of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 36, 40, 41, 42, 43, 44 under 35 U.S.C. 103 (a) in the immediately preceding paragraphs, thus Applicants are referred to these paragraphs for further explanation and arguments regarding Marumoto et al.

Claims 1, 9, 10, 13, 23, 31, 32, 33 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marumoto et al as applied to claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 36, 40, 41, 42, 43, 44 above, and further in view of Tavel (Tavel, Chest. 2001; 119: 907-925). The teachings of Marumoto et al. are discussed above. Marumoto do not teach co-administration of a stress echocardiography test during induced cardiac stress, nor do they teach the type of exercise testing used. Tavel teaches the coadministration of a stress echocardiography test during induced cardiac stress, (see whole document). Tavel teaches that treadmill or bicycle exercise testing are obvious variants (see p. 907, right column, 2nd paragraph). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Marumoto et al. by co-administering a stress echocardiography test, as taught in Tavel because according to Tavel, "exercise testing with ECG monitoring remains a cornerstone of cardiovascular evaluation" (p. 919, right column, 3rd paragraph). In addition, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Marumoto et al. by using either bicycle or treadmill testing, as taught in Tavel because states that either type of test can be used. The person of ordinary skill in the art would have been motivated to use ECG monitoring because it is already standard in the art, and for this reason as well, the person of ordinary skill in the art could have reasonably expected success. In addition, the person of ordinary skill in the art would have been motivated to use either a bicycle test or a treadmill because they are the most commonly performed stress tests (p. 907, right column, 2nd

paragraph). Furthermore, the person of ordinary skill in the art could have reasonably expected success for the same reasons. Thus the claims do not contribute anything non-obvious over the prior art. Thus the claims do not contribute anything non-obvious over the prior art.

Claims 1, 15, 16, 17, 23, 37, 38, 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marumoto et al as applied to claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 36, 40, 41, 42, 43, 44 above, and further in view of Raza et al. (Inter J Cardio. 2001; 31: 157-167). The teachings of Marumoto et al. are discussed above under Rejections under 35 USC 103. Marumoto et al. do not teach using pharmacological agents in lieu of exercise stress testing. Raza et al. teach the use of pharmacological stress induction (*e.g.*, dobutamine or adenosine). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Raza et al. by administering dobutamine or adenosine, as taught in Raza et al. because pharmacologic agents can be used in lieu of exercise in stress testing in cases where the patients are not able to exercise for medical reasons (p. 158, left column, 1st paragraph). The person of ordinary skill in the art would have been motivated to administer pharmacologic agents in cases where patients are too ill to perform the exercise test adequately. Furthermore, the person of ordinary skill in the art could have reasonably expected success because such methods of administering stress tests are old in the art and have a track record of success. Thus the claims do not contribute anything non-obvious over the prior art.

Applicants did not address the rejections under 35 U.S.C. 103(a) in their remarks other than to state that since Marumoto does not meet the claim limitations of 1 and 23, the rejections made under 35 U.S.C. 103(a) in the previous Office action (mailed 18 April 2006) fail. Since the rejection under 35 U.S.C. 102(b) was withdrawn, and a new rejection under 35 U.S.C. 103(a) was made over claims 1 and 23 (as well as others), this argument is moot. The rejection under 103(a) obviates but does not anticipate a claim.

New Claim Rejections Based on Articles Submitted for August 2006 IDS

Claim Rejections - 35 USC § 102

Claims 1, 2, 3, 4, 5, 6, 9, 10, 13, 18, 19, 20, 21 and 22, are rejected under 35 U.S.C. 102(b) as being anticipated by Nicholson et al. (Clin Exp Pharmacol Physiol. 1993; 20: 535-540—reference CT on IDS submitted on 18 August 2006). The claims recite a method of detecting coronary artery disease (CAD) in a human comprising measuring BNP in the human by immunoassay at baseline, inducing cardiac stress via exercise testing (treadmill or bicycle test), measuring BNP immediately post cardiac stress and about 10-15 minutes post-cardiac stress, calculating a relative change in the marker related to BNP wherein CAD is detected if the relative change after cardiac stress is greater than predetermined clinically effective values. Nicholson et al. teach a method of measuring BNP immunoassay at baseline (*i.e.*, a predetermined clinically effective threshold value—no other predetermined clinically effective threshold value is

defined in the specification) and also using ECG during stress testing in humans comprising inducing cardiac stress via exercise testing and measuring BNP immediately post cardiac stress and about 10-15 minutes post-cardiac stress and calculating the relative change in BNP measurements at different time-points and compared to normal subjects wherein BNP levels reflected ischemic heart disease (see p. 537, entire section under Study Protocol and Figure 1). Ischemic heart disease represents a pathological development in the course of coronary artery disease, thus inherently represents a stage in CAD. Applicants do not define the "predetermined clinically effective threshold value" in the specification as a number, but rather, in broad terms to indicate that the value may be adjusted depending upon whether one is seeking greater sensitivity or specificity of the clinical test (see [0058]). No number value is given, thus the resting BNP levels recorded in Nicholson et al. could serve as a threshold value. Claims 18-22 recite the method of claim 1, wherein: the relative change in the marker related to BNP is from about 10% (claim 18) 10% to about 400% (claim 19), at least about 1% per minute of exercise (claim 20), at least about 5% per minute of exercise (claim 21) and about 5% to about 27% per minute of exercise (claim 22). Because Nicholson et al. teach exactly the same method steps as recited in the instant claim 1, the limitations recited in claims 18-22 would by necessity inherently be met by Nicholson et al., although they are silent with respect to the specific values taught in the claim.

Claim Rejections - 35 USC § 103

Claims 1, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicholson et al. as applied to claims 1, 2, 3, 4, 5, 6, 9, 10, 13, 18, 19, 20, 21 and 22 above, and further in view of Tavel (Chest, 2001; 119: 907-925). The teachings of Nicholson et al. are discussed above under Rejections under 35 USC 102. Nicholson do not teach bicycle testing. Tavel teaches that treadmill or bicycle exercise testing are obvious variants (see p. 907, right column, 2nd paragraph). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Nicholson et al. by using either bicycle or treadmill testing, as taught in Tavel because states that either type of test can be used. The person of ordinary skill in the art would have been motivated to use either test because they are the most commonly performed stress tests (p. 907, right column, 2nd paragraph). Furthermore, the person of ordinary skill in the art could have reasonably expected success for the same reasons. Thus the claims do not contribute anything non-obvious over the prior art.

Claims 1, 15, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicholson et al. as applied to claims 1, 2, 3, 4, 5, 6, 9, 10, 13, 18, 19, 20, 21 and 22 above, and further in view of Raza et al. (Inter J Cardio. 2001; 31: 157-167). The teachings of Nicholson et al. are discussed above under Rejections under 35 USC 102(b). Nicholson et al. do not teach using pharmacological agents in lieu of exercise stress testing. Raza et al. teach the use of pharmacological stress induction

(*e.g.*, dobutamine or adenosine). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Nicholson et al. by administering dobutamine or adenosine, as taught in Raza et al. because pharmacologic agents can be used in lieu of exercise in stress testing in cases where the patients are not able to exercise for medical reasons (p. 158, left column, 1st paragraph). The person of ordinary skill in the art would have been motivated to administer pharmacologic agents in cases where patients are too ill to perform the exercise test adequately. Furthermore, the person of ordinary skill in the art could have reasonably expected success because such methods of administering stress tests are old in the art and have a track record of success. Thus the claims do not contribute anything non-obvious over the prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest, whose telephone number is571 272-4482. The examiner can normally be reached on Monday through Friday, 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on571 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest, Ph.D.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER